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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,613	07/31/2001	Susanna M. Rybak	15280-3431US	8380

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07/03/2003

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EXAMINER

YU, MISOOK

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/622,613

Applicant(s)

RYBAK ET AL.

Examiner

MISOOK YU, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16, 20-27, 31-39, 41 and 42 is/are pending in the application.
- 4a) Of the above claim(s) 20-27, 31-33 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 34-39, 41 and 42 is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11.
- 4) ☒ Interview Summary (PTO-413) Paper No(s). 21.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Sequence alignment.

DETAILED ACTION***Election/Restrictions***

The newly submitted amendment (Paper No. 17) and the new CFR changes isoleucine in the old SEQ ID NO:2 to asparagine (new SEQ ID NO:2) at amino acid position 21 of SEQ ID NO:2. Applicant states on the record that isoleucine at the position was inadvertent error during preparation of the national stage application and points the support in PCT/US99/06641 filed on 03-26-1999 and SEQ ID NO:2 is a species of the base claim 1. Since the newly submitted SEQ ID NO:2 fits the description of the base claim 1, claims 1-16 are rejoined for examination on merits.

This application contains claims 20- 27, and 31-33 drawn to an invention nonelected with traverse in Paper No. 15. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 20- 27, and 31-33 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-16, 20-27, 31-39, 41, and 42 are pending and claims 1-16, 34-39, 41, and 42 are examined on merits.

Specification

The disclosure objected is withdrawn in view of the amendment.

Information Disclosure Statement

A signed copy of the earlier IDS (Paper No. 11) is attached.

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Claim Rejections - 35 USC § 112

The rejection of claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is either moot or withdrawn in view of the amendment.

The rejection of claims 34-37 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn because the evidence in Dr. Susanna Rybak's Declaration under 37 C.F.R. § 132 is convincing.

The rejection of claim 38 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn because applicant's argument is convincing.

NEW GROUND OF REJECTION

Claim Objections

Claims 2-6, and 8-12 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The base claim 1 that claims 2-6, and 8-12 depend from is drawn to a protein with specific amino acids at 5 specific positions. However,

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claims 2-6, and 8-12 do not have those specified amino acids at the specified positions.

Claim Rejections - 35 USC § 112

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are interpreted as drawn to ribonucleases that meet the two criteria, i.e. with the specific amino acids at the specified positions recited in the base claim and with at least 60 % sequence identity (see the definition of "substantially identical" at page 10, lines 9-11 of the specification) to SEQ ID NO:2. The specification teaches several ribonucleases with all of them more than 99 % sequence identity to SEQ ID NO:2 but the specification does not teach any ribonuclease with 60 % sequence identity to SEQ ID NO:2 (about 100 amino acid protein) and still has ribonuclease activity. The specification does not teach which 40 amino acids or so could be changed without affecting the activity. It is the Office's position that protein chemistry is unpredictable, especially when 40 amino acids out of 100 amino acids are changed. For example, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from

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sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). Boix et al (IDS, 1996, J. Mol. Biol. Vol. 257, pages 992-1007) teach at the paragraph bridging page 992-3 that ribonuclease is mostly antiparallel beta structures and the beta structures and one alpha helix makes active site. The instant specification does not teach which 40 amino acids of instant SEQ ID NO2 could be changed without affecting the three dimensional structure important for the enzymatic activity. Further, The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen.

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These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. The specification provides insufficient guidance, and provides no working examples of at least 60 % sequence identity to SEQ ID NO:2 but still retains ribonuclease activity. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

Conclusion

The main problem of the instant application is that the instant SEQ ID NO:4, 8, 17, and 19 do not match any sequence in WO9950398-A2 publication (PCT/US99/06641) as discussed on 6-25-2003 over telephonic interview. See the attached sequence alignment. SEQ ID NO: 2, 6, 11, 13, 15, 21, and 24 have at least one identical sequence in WO9950398-A2 publication. It is recommended to use a computer software (the examiner is aware at least 2 easy to use commercially available softwares) to see if the new sequence to be submitted in an amendment is identical to those in PCT/US99/06641 in order to avoid further confusion and delay.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is

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filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


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Misook Yu

June 27, 2003



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